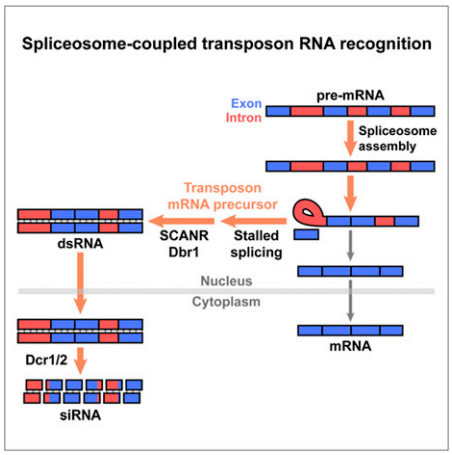
In This Issue

Cell



Stalled Spliceosomes Set Up siRNAs

PAGE 957

RNAi systems protect genomes from expressing foreign sequences like transposons. Dumesic et al. show that, in the yeast *Cryptococcus neoformans*, small-RNA-mediated suppression of these sequences hinges on the spliceosome. Pre-mRNAs containing suboptimal splicing signals, like those with transposons, accumulate on spliceosomes. These stalled complexes are substrates for a newly identified spliceosome-associated RNAi complex that generates siRNAs from the partially spliced messages, which then target the spliced "nonself" messages for degradation. These findings suggest that selfish genetic elements with weak splicing signals can be functionally distinguished from host genes and eliminated.

By AT-Hook or by Crook-ed Chromatin

PAGE 984

Rett syndrome is a neurodevelopmental disorder with variable severity caused by mutations in the MeCP2 gene. Baker et al. generate mouse models of Rett that show variability reminiscent of human patients, depending on whether a previously unrecognized AT-hook domain is disrupted. AT-hook domains are typical of proteins in the HMGA family, which alter chromatin structure. The results suggest that MeCP2 may contribute to the maintenance of chromatin structure in neurons and that this function is impaired in Rett syndrome.

Histone Mark Causal for Transcription

PAGE 1021

H3K4 trimethylation (H3K4me3) is a prominent histone mark found at promoters of actively transcribed genes. Lauberth et al. now show that H3K4me3 plays a causal role in transcription by recruiting the TAF3 subunit of TFIID to promoters and facilitating the assembly of the transcriptional preinitiation complex. Importantly, H3K4me3 performs these roles even in the absence of a TATA box. The study further suggests that H3K4me3 is required at promoters of rapidly induced genes, including cell-cycle genes and some p53 targets.

Jumonji Adds a String to Its Bow

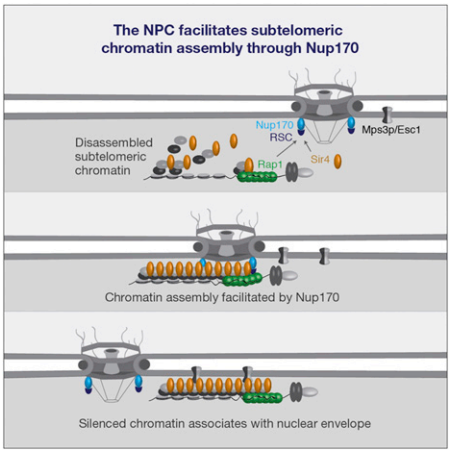
PAGE 1037

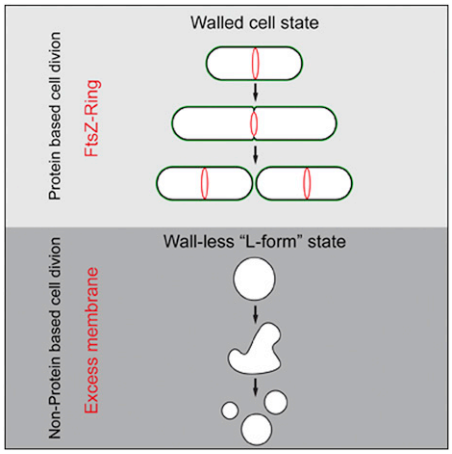
Reprogramming of somatic cells into induced pluripotent stem cells is an inefficient process involving epigenetic changes, prompting a search for inhibitors of reprogramming. Zhao et al. show that Jmjd3 inhibits reprogramming via two mechanisms. Through its histone demethylase activity, it promotes expression of Ink4a/Arf. And through a newly identified demethylase-independent activity, it promotes the ubiquitination and degradation of a protein that is required for the expression of Oct4 and for reprogramming.

Nup-tials between Telomeres and Nuclear Envelopes

PAGE 969

Although interactions between the nuclear pore complex (NPC) and chromatin are well known, the role of the NPC in gene expression is not fully understood. Van de Vosse et al. demonstrate that the NPC protein Nup170p, via interactions with the silencing factor Sir4p, associates with subtelomeric regions of the yeast genome, where it represses gene transcription, regulates nucleosome positioning, and promotes telomere tethering to the nuclear envelope. The findings suggest that Nup170p may propagate a repressed chromatin state by defining heterochromatin structure.





Lipids Drive Cell Division, L Yes!

PAGE 997

Cell-wall-deficient "L-form" bacteria divide by membrane blebbing or tubulation independent of the protein-based division machinery used by normal bacteria cells. Mercier et al. show that mutations enable L forms to grow simply by upregulating membrane synthesis. Moreover, artificially increasing membrane surface area in wild-type protoplasts leads to L-form-like division. The similarity of L-form proliferation to the in vitro reproduction of membrane vesicles suggests that L forms may provide a model for evolution of membrane-bound cellular life on earth.

Targeting the Tumor-Stroma Interface

PAGE 1065

Medulloblastoma is the most common malignant brain tumor of children. Snuderl et al. show that placental growth factor (PlGF), produced by the cerebellar stroma, and its receptor neuropilin 1 (Nrp1) are required for medulloblastoma growth, whereas their inhibition suppresses tumor growth. Notably, PlGF action in promoting medulloblastoma appears to be distinct from the angiogenic role that it plays in other cancers. The results suggest that targeting tumor-stroma interactions, via inhibition of PlGF or Nrp1, could provide an alternative therapeutic approach for the treatment of medulloblastomas.

Vulnerability for Peripheral Nerve Sheath Tumors

PAGE 1077

Malignant peripheral nerve sheath tumors (MPNSTs) are soft-tissue sarcomas that occur sporadically in a subset of patients with neurofibromatosis type 1. They are highly aggressive, therapeutically resistant, and typically fatal. Mo et al. find elevated expression of the chemokine receptor CXCR4 and its ligand CXCL12 in murine and human MPNSTs and show that CXCR4 depletion or pharmacological inhibition blocks MPNST proliferation by downregulating cyclin D1, causing cell-cycle arrest. CXCR4 thus represents a potential therapeutic target for the treatment of MPNSTs.

Dueling E3s Stabilize the Circadian Clock

PAGE 1091 and PAGE 1106

CRYPTOCHROME (CRY) repressor proteins are key players in the negative feedback loop of the circadian clock. In this issue, Yoo et al. and Hirano et al. identify FBXL21, an F-box-type ubiquitin E3 ligase, as a regulator of CRY1 and CRY2. FBXL21 has the opposite effects on circadian period and CRY stability compared to FBXL3, a previously known E3 ligase for CRY degradation. Their findings demonstrate that the combined antagonistic actions of FBXL21 and FBXL3 provide stable oscillation of the circadian clock.

Origin-Specific Tag for Neuronal Messenger

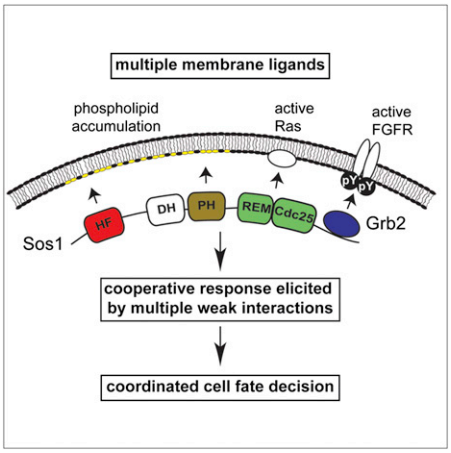
PAGE 1119

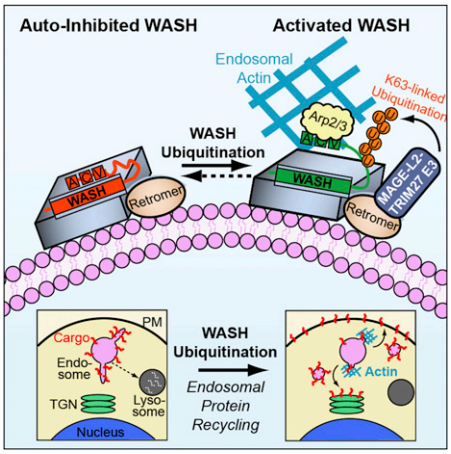
The NMDA receptors signal to transduce information from neuronal processes back to the cell nucleus. These receptors reside both within synapses and outside of synaptic regions, and signal transduction from each class had different cellular outcomes. Karpova et al. report that the spatial origin of an NMDAR signal is encoded by the differential phosphorylation and nuclear transport of a messenger protein, Jacob.

Suboptimal but Somehow Just Right

PAGE 1008

Protein domain complexity has increased throughout eukaryotic evolution. To understand the reasons for this trend, Findlay et al. study the signaling functions of the multidomain Sos1/Grb2 complex, which integrates signals from various protein and phospholipid ligands to control differentiation during mammalian embryogenesis. The results suggest that the ligand-binding domains of Sos1-Grb2 are tuned not for maximal affinity but for functional cooperativity, suggesting that complex domain organization in metazoans facilitates coordinated cell fate decisions during development.





U-B-Quitin' That WASH to go Retro?

PAGE 1051

Trafficking of proteins from the plasma membrane and Golgi back to the ER is mediated by the Retromer complex. Hao et al. find that a component of this complex is an E3 ligase that transfers K63-linked ubiquitin chains to the actin nucleation factor WASH, relieving its autoinhibition to activate actin nucleation and drive trafficking. These findings illustrate a role for nondegradative ubiquitination in the regulation of actin nucleation, endosomal sorting, and organelle homeostasis.

SRP Loses Monopoly on Secretion

PAGE 1134

Translocation into the endoplasmic reticulum (ER) is an essential step in the biogenesis of secreted proteins, involving in many cases a well-studied pathway mediated by the signal recognition particle (SRP). Now, Ast et al. systematically assess secreted yeast proteins and find that a significant portion does not rely on SRP. In the case of GPI-anchored proteins, a network of cytosolic chaperones and ER targeting factors guides translocation, highlighting the varied signals and pathways that contribute to secretome biogenesis.

C-ing Variants

PAGE 1146

Tet proteins oxidize 5-methylcytosine (mC) to generate 5-hydroxymethyl (hmC), 5-formyl, and 5-carboxylcytosine. Spruijt et al. identify proteins that bind to all of these derivatives in mouse ES cells. They show that mC and hmC recruit a distinct and only partially overlapping set of proteins in ES cells, neuronal progenitor cells, and the adult mouse brain. The identified readers suggest a role for mC derivatives in active DNA demethylation as well as a DNA demethylation-independent function.

Connections between Ubiquitin Family Modifiers

PAGE 1160

Posttranslational modifications profoundly affect protein stability and function. In this Resource, Merbl et al. profile ubiquitin family modifications in mammalian cells, identifying more than 1,500 putative targets. The targets provide information on substrates regulated by ubiquitin-like molecules and their interconnections and reveal an unexpected role for the ubiquitin-like modifier FAT10 in mitotic control.

Immunoproteasome Properties Revisited

PAGE 1184

Immunoproteasomes have been previously proposed to degrade ubiquitinated proteins more efficiently than the constitutively expressed proteasome. Nathan et al. challenge this earlier conclusion, finding that purified immuno- and constitutive proteasomes bind and degrade polyubiquitinated proteins at similar rates and that immunoproteasomes do not protect against IFNγ-dependent inflammatory responses.

Dead CRISPR Kills Expression

PAGE 1173

Cas9/CRISPR technology has recently been demonstrated to achieve site-selective genome engineering. Qi et al. now repurpose this CRISPR method to control gene expression by coupling a catalytically inactive version of Cas9 to a complementary small guide RNA. They show the repression of transcription of specific target genes without detectable off-target effects in both bacteria and human cells. This CRISPR interference system has the potential for, among other applications, large-scale parallel and reversible transcriptome manipulation.